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REVIEW

Macronutrients and the Adipose-Liver Axis in Obesity and Fatty Liver

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SUMMARY

The present review addresses the complex role of carbohydrates (simple and complex) and fats (saturated, unsaturated, polyunsaturated) in the pathogenesis of nonalcoholic fatty liver disease. Specifically the review focuses on the liver–adipose tissue axis in this disease and the role each nutrient class plays in the crosstalk between the liver and the adipose tissue and the pathophysiology of nonalcoholic fatty liver disease.

Macronutrient metabolism is a highly orchestrated process, with adipose tissue and liver each playing central roles in nutrient uptake, processing, transport, and storage. These 2 tissues form an important metabolic circuit, particularly as it relates to lipids as the primary storage form of excess energy. The function of the circuit is influenced by many factors, including the quantity and type of nutrients consumed and their impact on the overall health of the tissues. In this review we begin with a brief summary of the homeostatic disposition of lipids between adipose tissue and liver and how these processes can become dysregulated in obesity. We then explore how specific dietary nutrients and nutrient combinations can exert unique influences on the liver–adipose tissue axis. *(Cell Mol Gastroenterol Hepatol 2019;7:749–761; https://doi.org/10.1016/j.jcmgh.2019.02.001)*

Keywords: Carbohydrate; Fat; Metabolism; Diet; Fatty Liver Disease.

Macronutrient Flux Through Adipose Tissue and Liver

When a healthy individual consumes dietary fat, the lipids are converted to triglyceride within the intestine and packaged into chylomicrons for delivery to peripheral tissues (primarily muscle and adipose tissue) (Figure 1). When chylomicrons reach their target tissues, fatty acids are released through the local action of lipoprotein lipase (LPL). Adipose tissue is reasonably efficient at extracting free fatty acids (FFA) from chylomicrons for uptake and storage; however, there is some "spillover" of FFA into the circulation (33%–36% of the total delivered), which then become available for uptake by the liver.[1] The chylomicron remnants that are left after LPL-mediated triglyceride lipolysis also contain a small proportion of their original triglyceride content. Spillover FFA and chylomicron remnants represent 2 routes by which dietary fat can gain direct access to the liver. Stable isotope studies indicate that in normal individuals, dietary fat accounts for approximately 15% of the triglyceride present in the liver at any given time.[2]

When a healthy individual consumes carbohydrate, any substrate in excess of that needed to fulfill short-term metabolic need is converted into fatty acid through de novo lipogenesis (DNL). DNL takes place in both the liver and adipose tissue (reviewed in[3,4]). The fatty acid products of DNL are esterified into triglyceride for storage; the primary reservoir for stored lipids is in adipose tissue, and thus the triglyceride produced in adipose tissue is stored directly. In the liver, some newly synthesized triglyceride is stored locally, but most is packaged into very low density lipoproteins (VLDL) for export to adipose tissue.[5] Adipose tissue extracts lipid from VLDL in the same fashion as it does from chylomicrons, using LPL. When carbohydrates and lipids are consumed simultaneously, adipose tissue is called on to import glucose for DNL and take up lipids from both chylomicrons and VLDL. Insulin, induced by dietary carbohydrate, helps adipose tissue accommodate the substrate load by increasing cell-surface expression of the GLUT4 glucose transporter[6] and increasing adipose tissue LPL activity.[7]

During fasting, adipose tissue becomes a net exporter rather than importer of lipid. When nutrients and insulin are sparse, adipocytes hydrolyze their intracellular triglycerides using hormone-sensitive lipase and release FFA for uptake by several tissues including the liver. Indeed, 59% of the triglyceride in a normal liver derives from FFA taken up from the circulation.[2] In obesity, the situation in adipose tissue resembles fasting: although insulin levels are adequate or even high, adipocytes can no longer respond to the anabolic effects of the hormone, so they instead behave as though they are insulin-deficient, hydrolyzing intracellular triglyceride and releasing FFA into the circulation. To

Abbreviations used in this paper: **DNL, de novo lipogenesis; ER, endoplasmic reticulum; FFA, free fatty acid; FGF21, fibroblast growth factor-21; LPL, lipoprotein lipase; MUFA, monounsaturated fatty acid; NAFLD, nonalcoholic fatty liver disease; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; VLDL, very-low-density lipoprotein.**

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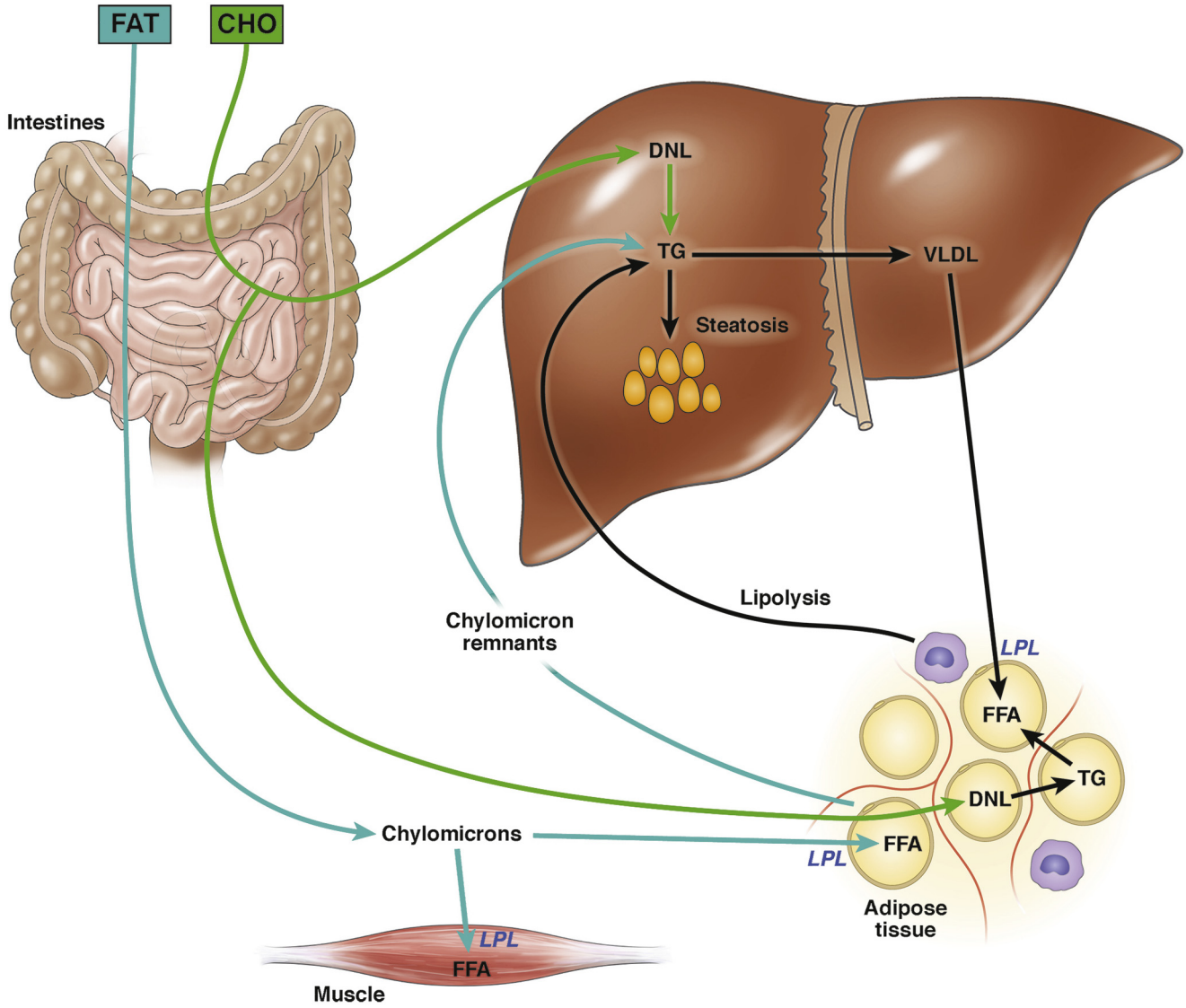

Figure 1. Route of dietary carbohydrates and fats to the liver and adipose tissue. Dietary carbohydrate enters the portal circulation from the intestine and enters the liver. Excess substrate not needed for metabolism is converted to fatty acid via DNL and incorporated into triglyceride. Triglycerides are exported from the liver as VLDL, where they are delivered to adipose tissue, where they are broken down into FFA by the enzyme LPL and stored. Dietary fat is packaged into chylomicrons in the intestine and delivered initially to muscle and adipose tissue. Any lipid remaining in the chylomicron remnants are routed to the liver, as are "spillover" FFA not taken up by adipocytes. CHO, carbohydrate; TG, triglyceride.

make matters worse, insulin resistance also suppresses the ability of adipocytes to take up lipid from chylomicrons and VLDL. This leads to further increases in circulating FFA, which are then diverted to other tissues including the liver, where they are stored as ectopic lipid. Overall, alterations in nutrient flux through the adipose-liver circuit play a key role in the pathogenesis of fatty liver disease. Dietary carbohydrates exert a direct influence on the liver through DNL; carbohydrates and fats can also contribute indirectly to fatty liver by increasing adipose tissue lipid stores that are subsequently mobilized through lipolysis.

The adipose tissue–liver metabolic circuit is sensitive not only to the total amount of calories consumed but also the distribution of calories across macronutrient classes (carbohydrates and fats) and even to individual types of macronutrients. The following sections explore the impact of specific nutrients and nutrient combinations on adipose tissue and liver health.

The Influence of Obesity on the Adipose-Liver Axis

Under normal physiological conditions the liver and adipose tissue strive to maintain metabolic homeostasis through the secretion of adipokines and growth factors.[8,9] Under conditions of nutrient excess this communication is disrupted, contributing to metabolic derangement and related injury to both organs.

Looking first at adipose tissue, obesity prompts an increase in tissue mass through a combination of adipocyte hypertrophy and hyperplasia. This enlargement increases oxygen consumption and strains oxygen delivery to the tissue,[10,11] which results in cell death and the associated recruitment of inflammatory cells from the circulation.[12-14] Diseased adipocytes also undergo changes in adipokine production: for example, adiponectin, which promotes physiological lipid storage in fat and lipid oxidation in muscle and liver, is significantly decreased in obesity.[15] In contrast, inflammatory cytokines and chemokines, such as tumor necrosis factor, interleukin-6, monocyte chemoattractant protein-1 (CCL2), and others, are produced in increased amounts by adipocytes (reviewed in[8]).[16-20] Tumor necrosis factor and interleukin-6 impair responsiveness to insulin.[21,22] This interferes with the ability of adipocytes to take up fatty acids from the circulation, and furthermore induces the hydrolysis of intracellular triglycerides, which leads to the systemic release of more fatty acids. Cytokines also promote the recruitment of inflammatory cells to adipose tissue, which inflict further damage, thus perpetuating adipose tissue dysfunction.[20,23,24] Overall, the dysregulation of metabolic and immunoregulatory adipokines in dysfunctional adipose tissue results in the rerouting of fatty acids to other "ectopic" tissues, including the liver.

The principal compound secreted by the liver that influences the adipose-liver axis is fibroblast growth factor-21 (FGF21). FGF21, produced by hepatocytes, promotes glucose uptake and energy expenditure in white adipose tissue.[25] In response to FGF21, adipose tissue secretes adiponectin, which then circles back to the liver to facilitate insulin signaling.[26] In obesity, hepatic production of FGF21 is upregulated.[9] Its action toward white adipose tissue, however, is blunted.[27] FGF21 rises even further with the development and progression of hepatic steatosis,[28,29] underscoring how obesity interferes with another fundamental circuit intended to maintain metabolic homeostasis.

The Influence of Specific Dietary Macronutrients on the Liver and Adipose Tissue

It is well established that consumption of excess calories is a major factor in the development of obesity and fatty liver disease, particularly when coupled with genetic predispositions and a sedentary lifestyle. There is also information indicating that the composition of a diet, independent of its caloric content, can exert a unique influence on the well-being and function of adipose tissue and liver. In this section we highlight the role of macronutrients in nonalcoholic fatty liver disease (NAFLD) pathogenesis, paying particular attention to their effect on adipose-liver interactions. The discussion is organized by macronutrient class, specifically highlighting carbohydrates and fats. Although we focus on macronutrients 1 group at a time, it is important to keep in mind that the human diet constitutes a mixture of carbohydrates, fats, and proteins. The standard human diet comprises 40%–50% carbohydrate, 30%–40% fat, and 20% protein. The interactions among macronutrient classes can themselves be biologically important, and we highlight these in select cases.

Dietary Carbohydrates

Carbohydrates are designated as simple or complex based on the number of sugar molecules they contain (monosaccharides and disaccharides vs polysaccharides). Individual carbohydrates differ in their abilities to induce DNL,[30-32] which plays a role in their tendency to provoke fatty liver and more serious forms of liver injury. Numerous studies have investigated the role of dietary carbohydrates in NAFLD pathogenesis. Less information is available on the role of dietary carbohydrates on adipose tissue in the context of NAFLD.

Simple Carbohydrates. Simple carbohydrates (sugars) include the dietary sweeteners glucose, fructose, and sucrose. Glucose and fructose are monosaccharides, whereas sucrose is a disaccharide comprised of glucose and fructose. Glucose and fructose are readily absorbed by the small intestine. Until recently, both molecules were believed to be transported directly from the intestine to the portal circulation for delivery to the liver; however, new evidence indicates that fructose is metabolized by the intestine and enters the portal circulation only when consumed in amounts sufficient to saturate this metabolic capacity.[33] Glucose and fructose molecules that do make their way into the portal circulation are taken up by the liver. Both sugars stimulate DNL, which under conditions of excess can lead to hepatic steatosis. Importantly, the DNL reaction yields palmitate, a toxic long-chain saturated fatty acid (SFA); once generated, palmitate must be promptly desaturated and incorporated into triglyceride, or it can cause hepatocellular injury (discussed in the saturated fat section). Fructose is a potent inducer of DNL because of the lack of feedback regulation of its metabolism by fructokinase (reviewed in [34]). Fructose metabolism stimulates more hepatic lipid production than glucose; it also consumes ATP and generates uric acid as a by-product.[35] Furthermore, fructose metabolism yields toxic carbonyls that can damage mitochondria.[36] This combination of events, combined with the generation of SFA, can lead to liver injury through endoplasmic reticulum (ER) stress and hepatic mitochondrial dysfunction.[37-40] The heightened toxicity of fructose compared with glucose has been demonstrated in multiple studies involving animals and humans. Work from our laboratory showed that fructose, when used as the carbohydrate in a methionine-choline-deficient diet, induced twice the degree of liver injury than glucose.[41] Others found that in mice fed a high-fat diet, fructose rather than glucose in the drinking water led to more microvesicular hepatic steatosis and more activation of the stress kinase Jun N-terminal kinase in the liver, which are both predictors of greater liver injury.[42] In human subjects, consumption of fructose-sweetened beverages but not glucose-sweetened beverages for 10 weeks induced mild liver injury as evidenced by elevated serum γ-glutamyl transpeptidase along with elevations in several circulating inflammatory molecules.[43,44] Furthermore, epidemiologic studies confirm that long-term fructose consumption is associated with serious hepatic outcomes including steatohepatitis and liver fibrosis.[45-47]

Although most ingested fructose is metabolized by the liver, fructose can also be used by other organs including adipose tissue. Studies of adipocytes in culture show that fructose, but not glucose, has a trophic effect on the cells, stimulating the expansion of adipocyte precursors.[48] Not surprisingly, fructose metabolism by adipocytes also promotes lipogenesis, leading to storage of some of the fatty acids and the release of some as FFA.[49] Studies have shown that fructose, but not glucose, consumption causes insulin resistance.[32,42] This acts as an ongoing stimulus to lipolysis in fructose-exposed adipose tissue. Moreover, the uric acid produced during fructose metabolism can inflict damage on adipocytes, stimulating oxidant stress and the production of inflammatory cytokines.[50,51] Overall, the adverse effects of fructose on adipocytes compound its adverse effects on the liver, by causing adipose inflammation and preventing proper adipose tissue lipid storage resulting in diversion of fatty acids to the liver (Figure 2).

The effects of glucose on liver and adipose tissue are generally milder than fructose, although overconsumption of glucose is not without consequence. Like fructose, glucose promotes DNL, which yields SFAs that are esterified and stored in adipose tissue and liver. Studies in mice indicate that glucose and fructose induce similar degrees of hepatic lipid accumulation when incorporated into isocaloric diets.[41,42] Similarly in humans, when identical amounts of glucose or fructose are fed to human subjects for periods up to 4 weeks, both sugars induce comparable increases in liver fat content.[52-54] Because the lipogenic properties of glucose and fructose seem similar, the increased harm from fructose in humans is likely related to ATP depletion and uric acid production and their downstream consequences.

One important point to note about dietary sugars is that their ability to induce liver injury is modulated by the fat present in the diet. Specifically, saturated fat induces DNL independently of dietary sugar,[55] so when sugar and saturated fat are consumed together, the DNL effect is magnified. This synergy is most evident when sugar (as the DNL substrate) is highly abundant in the diet. Our group showed that sugar + saturated fat, when fed to mice in a ratio of 60:20, induced significantly more DNL, hepatic steatosis, and liver injury than an equivalent combination of sugar + unsaturated fat.[56,57] This synergy was not seen when sugar + saturated fat were fed in a ratio of 40:40.[58]

Complex Carbohydrates. Complex carbohydrates (starches, glucans, fructans, and cellulose) are polysaccharides with a range of structures and physical properties. Glucans, fructans, and cellulose, along with a subset of starches that are highly resistant to enzymatic digestion, are often grouped into a single category under the term "dietary fiber." The impact of starches and fiber on adipose tissue and liver is dependent in part on their metabolism by the host, but also on their metabolism by microbes residing in the gut.

Starches. Starches are polymers of glucose with different chain lengths and α-glycosidic linkages. Like all polysaccharides, they require enzymatic digestion before absorption. However, because of their size and structure they are not completely degraded to monosaccharides or disaccharides in the small intestine and as a result are less "glycemic" than simple sugars. Because starch yields lower blood concentrations of glucose than sugar, it is less likely to stimulate lipogenic genes in the liver; furthermore, it provides less substrate for fatty acid synthesis. The blunted lipogenic effect of dietary starch compared with sugar has been demonstrated in direct comparisons of the 2 carbohydrates in mice.[59] Even within the category of dietary starches there are variations in the ability of individual polysaccharides to stimulate hepatic lipogenesis depending on the ease with which they are digested.[60] The impact of high-glycemic (digestible) and low-glycemic (resistant) starches on adipose tissue have also been investigated in select studies.[61,62] As expected, high-glycemic starches induced more adipose tissue enlargement than low-glycemic starches. At present there is little information available about the effect of dietary starches on adipose tissue inflammation.

Fiber. Fiber is either very resistant to enzymatic digestion in the intestine, or in the case of β-linked plant polysaccharides (β-glucans and cellulose), cannot be digested at all by the intestine. These resistant polysaccharides make their way to the colon, where they undergo fermentation by colonic bacteria.[63] Fermentation of fiber yields the short-chain fatty acids acetate, butyrate and propionate; some of these are used by the bacteria themselves, but some are also absorbed into the portal circulation where they have immediate access to the liver.[64] Hepatic extraction of short-chain fatty acids is efficient but incomplete. This enables some fatty acids to enter the systemic circulation[65] where they can exert independent influences on adipose tissue. Focusing on the liver first, it is important to note that short-chain fatty acids have several effects on hepatic metabolism that can either promote or prevent NAFLD. Butyrate stimulates fatty acid oxidation and thus should be beneficial to the liver.[66] In contrast, acetate is a substrate for hepatic lipogenesis[67] and propionate stimulates gluconeogenesis,[68] which should have an overall adverse effect. A recent mouse study disputes the prospect of harm by demonstrating that supplemental short-chain fatty acids prevent, rather than promote, experimental fatty liver disease.[69] Overall it remains unclear whether the net effect of short-chain fatty acids on the liver is beneficial or detrimental in the pathogenesis of NAFLD, although experts are leaning toward a salutary role for these compounds.[70] With respect to adipose tissue, short-chain fatty acids are believed beneficial to metabolic homeostasis. Animals and cell culture studies demonstrate that short-chain fatty acids promote adipocyte development and fat accumulation, stimulate adipokine production, and decrease lipolysis.[71-74] Human studies, although correlative, indicate that diets that increase circulating levels of short-chain fatty acids also reduce systemic circulating fatty acid concentrations, suggesting a suppressive effect on adipose tissue lipolysis.[75]

Dietary Fats

Dietary fats are consumed largely as triglycerides. Fats are named for the dominant type of fatty acid within the triglyceride molecule: SFAs, monounsaturated fatty acids

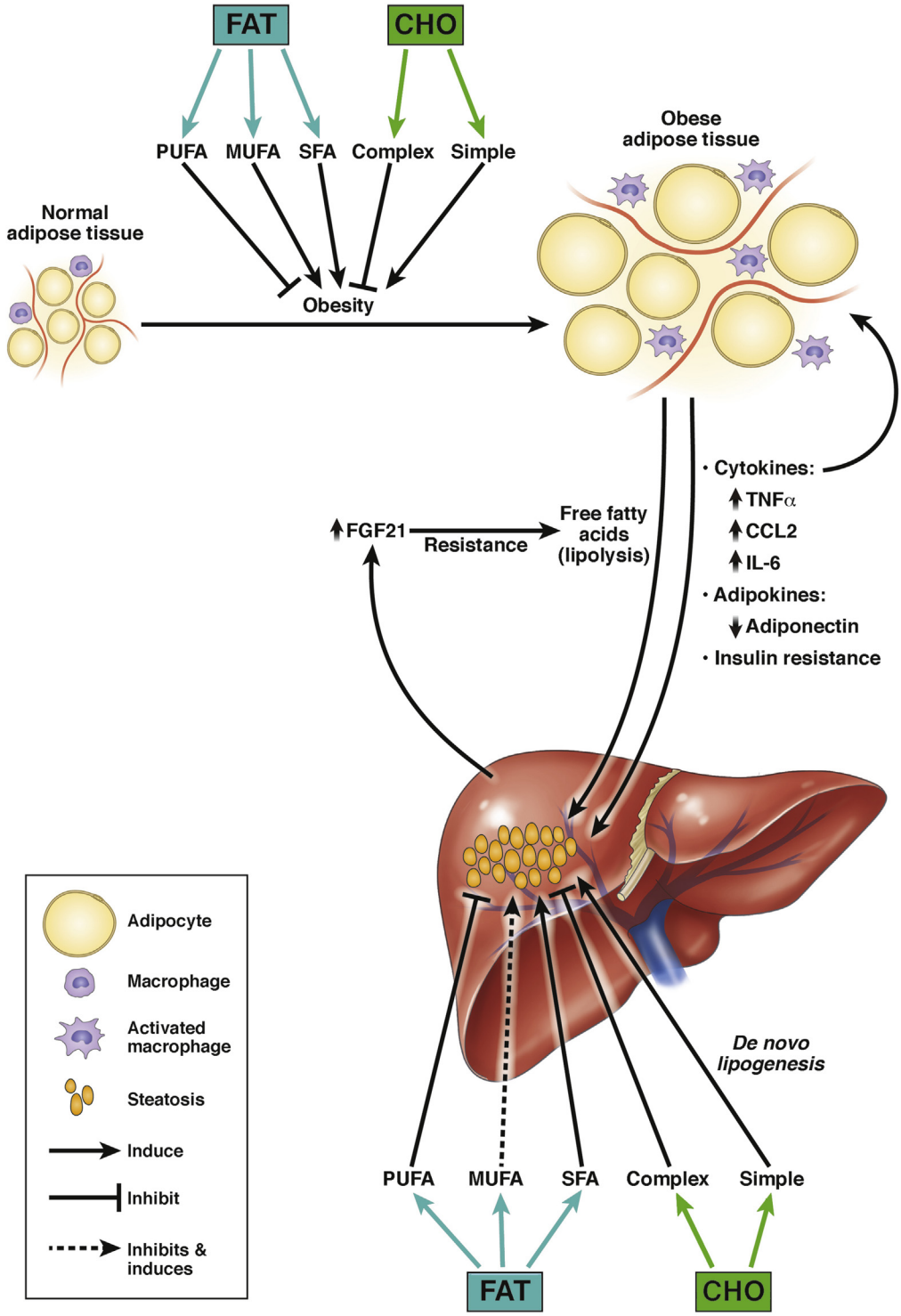

Figure 2. Endocrine interactions between liver and adipose tissue and the influence of macronutrients. Under conditions of dietary excess/obesity, adipose tissue adiponectin production declines and several proinflammatory cytokines and chemokines are upregulated. This can promote inflammation and insulin resistance in both tissues. FGF21 is upregulated in the liver, but its action is inhibited, preventing energy expenditure in adipose tissue and promoting lipolysis. The general contribution of individual macronutrients to the dysfunction of adipose tissue and liver in obesity and NAFLD is shown schematically (see text for details). CHO, carbohydrate; IL, interleukin; TNF, tumor necrosis factor.

(MUFA) or polyunsaturated fatty acids (PUFA). Dietary fat is taken up by tissues in the form of fatty acids after lipolysis of triglycerides at the cell surface. Fats are primarily incorporated into adipose tissue; they have secondary access to the liver via chylomicron remnants or spillover of excess FFAs into the circulation (Figure 1). The biologic effects of dietary fats are attributable to their component fatty acids, which are the main focus of the following summary.

Saturated Fats. Saturated fats and their component SFA come primarily from animal sources (meat and dairy). The SFA present in these foods are typically long-chain species containing 16 or more carbon atoms. Long-chain SFA are considered the most harmful of dietary fats because they

Table 1. Types of Monounsaturated Fatty Acid Used in Individual Animal and Human Studies

Reference	Author	Species	Dietary monounsaturated fatty acid	Notes
58	Duwaerts et al	Animal	High-oleate sunflower oil	
111	Hoefel et al	Animal	Olive oil	
112	Sampath et al	Animal	Triolein	
113	Meneses et al	Human	Olive oil–enriched mayonnaise, nuts	LIPGENE Study
114	Bozzetto et al	Human	Olive oil	
115	Ryan et al	Human	Olive oil, nuts, olives, fish	Mediterranean
116	Properzi et al	Human	Olive oil, nuts, fish	Mediterranean

have toxic effects on many types of cells; this is in contrast to medium-chain SFA, which are more inert and can even be beneficial to metabolic health.[76,77] Although medium-chain SFA are less toxic than long-chain SFA they are only minor components of standard meat and dairy items. However, they are enriched in a limited number of natural foods, such as coconut and palm kernel oils. Focusing on long-chain SFA because of their prevalence in the standard human diet, these SFA can directly injure hepatocytes through a variety of mechanisms including death receptor signaling, the induction of ER stress leading to intrinsic mitochondrial apoptosis, stimulation of toll-like receptors, activation of inflammasomes, and impairment of autophagy (reviewed in[78]).[79-88] SFA are also detrimental to adipocytes. They enhance adipocyte oxygen consumption, which contributes to adipose tissue hypoxia in vivo,[10,11,89] and in similar fashion to hepatocytes they cause ER stress, activation of toll-like receptor and nuclear factor-κB, which results in cell death and the production of proinflammatory cytokines.[90-97] The adverse effects of SFA-enriched diets on liver and adipose tissue have been documented in many studies in experimental animals.[11,88,98-102] In contrast, relatively few research groups have challenged human subjects with saturated-fat diets in the context of a controlled clinical trial. The available data from short-term human studies comparing dietary saturated fats with polyunsaturated fats indicate that saturated fats have a greater tendency to induce insulin resistance, hepatic steatosis, and a proinflammatory state characterized by elevated serum concentrations of tumor necrosis factor and interleukin-1-receptor antagonist.[103-106]

Although there is little doubt that SFA are cytotoxic, the toxicity of SFA toward liver cells in vivo seems dependent on their origin from the diet or DNL. This observation comes from studies from our laboratory investigating the hepatotoxicity of different combinations of dietary sugars and fats in mice. We reported that dietary tripalmitin, despite being comprised exclusively of SFA, caused only mild liver injury unless paired with sucrose.[56] This suggests that DNL SFA are more toxic than dietary SFA, which corroborates evidence in humans that fatty liver disease is related to excessive DNL.[2,107]

Unsaturated Fats. Unsaturated fats, which comprise MUFA and PUFA species, are the principal fats present in plants, seeds, nuts, and fish. The dominant dietary MUFA is oleic acid, which is abundant in olive oil. The dominant dietary PUFAs are linoleic acid (ω-6 PUFA) and α-linolenic acid (ω-3 PUFA) found in seeds and vegetables; other important dietary ω-3 PUFAs are the very long chain species eicosapentaenoic acid and docosahexaenoic acid, which can be produced from α-linolenic acid or obtained directly from a diet containing fish.[108] In general, unsaturated fats are considered healthier than saturated fats for the liver and adipose tissue. Still, there are properties that distinguish MUFA from PUFA, so the 2 classes are summarized individually.

Monounsaturated Fatty Acid. MUFA, unlike SFA, exert little toxicity toward liver or adipose tissue cells.[84,88,91,97,109,110] In fact, MUFA have been reported to promote adipocyte hyperplasia rather than the less desirable cellular enlargement in vivo, in association with blunted expression of inflammasome components and activation of metabolic pathways that portend improved insulin sensitivity.[99] Interestingly, despite the apparently benign nature of dietary MUFA toward hepatocytes and adipocytes in vitro, some studies indicate that MUFA-enriched diets (see Table 1 for ingredients) induce more hepatic steatosis than isocaloric SFA-enriched diets.[58,111,112] Pertinent to this point, studies from our laboratory showed that mice fed diets containing 40% kcal MUFA in the form of high-oleate sunflower oil for 6 months developed substantial hepatic steatosis coincident with pronounced adipose tissue injury and inflammation.[58] In 1 human study, feeding a high concentration of MUFA (44% kcal) for 12 weeks also induced monocyte chemoattractant protein-1 expression in adipose tissue.[113] This raises questions as to whether MUFA are truly nontoxic in vivo, particularly when used in high concentrations in the diet. In humans with NAFLD, the effects of MUFA-enriched "Mediterranean" diets have been explored in a small number of carefully controlled clinical trials. In 2 studies, subjects were fed a MUFA-enriched diet (40% total kcal fat) or a lower-fat nonenriched diet (30% total kcal fat) for 6–8 weeks.[114,115] In both cases the MUFA-enriched diet substantially reduced hepatic steatosis and improved insulin sensitivity more than the comparison diet, but other measures were equivalent. A third study was recently published that tested similar diets for 12 weeks. Unlike the earlier studies, this one showed improvement in hepatic steatosis with both the MUFA-enriched diet and the low-fat diet, with no significant difference between the 2.[116] Experts are now calling for further investigation of MUFA-enriched diets in patients with NAFLD that include extended treatment intervals and robust liver and adipose tissue outcome measures.[117] One important caveat is that Mediterranean

diets, although enriched in MUFA, may also contain higher levels of PUFA than comparison diets. This can make it difficult to assign any benefit of a Mediterranean diet specifically to MUFA. Until further evidence is collected, the specific benefit of MUFA for metabolic health remains uncertain.

Polyunsaturated Fatty Acid. PUFA are generally characterized as beneficial to metabolic health, particularly in relation to SFA. PUFA, however, are divided into 2 major subspecies (ω-3 and ω-6 PUFA) that can have different effects on tissue biology. For example, ω-3 PUFA can suppress inflammation through the generation of specialized pro-resolving mediators,[118] whereas ω-6 PUFA can promote inflammation by conversion to arachidonic acid and other inflammatory eicosanoids[119] (reviewed in[120]). The average Western diet contains far less ω-3 PUFA than ω-6 PUFA.[108,120,121] Consequently, efforts are underway to encourage incorporation of more ω-3 PUFA into the diet or the use of ω-3 PUFA supplements, or both.[121] Among the beneficial effects of PUFA, regardless of subspecies, are their ability to suppress lipogenesis and stimulate fatty acid oxidation by downregulating sterol regulatory element-binding protein-1, carbohydrate-responsive element-binding protein, and farnesoid X receptor and activating peroxisome proliferator-activated receptor-α.[122-125] In addition, ω-3 and ω-6 PUFA have both been shown to suppress nuclear factor-κB, inflammasome activation, and promote autophagy in hepatocytes.[126,127] Similarly, ω-3 and ω-6 PUFA are both capable of suppressing adipocyte hypertrophy and preventing inflammation and fibrosis in adipose tissue,[91,95,128,129] although there may be some selective benefit of ω-3 over ω-6 PUFA.[129] In a study of mice in vivo, ω-3 PUFA supplementation could prevent and reverse high-fat diet-induced hepatic steatosis.[130] Although in another study ω-6 PUFA did not achieve the same reduction in liver fat,[100] ω-3 and ω-6 PUFA both seem capable of preventing diet-induced insulin resistance and avoiding the diet-induced ER stress and inflammatory changes in the liver that occur with SFA-enriched diets.[100,130] In humans, some trials have compared PUFA-enriched diets (ω-3 or ω-6) with diets with other fats,[113,131,132] but many more have evaluated the effects of ω-3 PUFA supplements on subjects with fatty liver disease. The results of these trials are elegantly summarized in 2 recent reviews.[108,121] The consensus opinion is that although some studies report an advantage of ω-3 PUFA supplementation, overall outcomes are variable, and the promise of a therapeutic benefit is dampened by safety concerns related to bleeding and interactions with anticoagulant medications. Until further studies can verify the efficacy of ω-3 PUFA supplements as a therapeutic for NAFLD, experts still recommend incorporating more ω-3 PUFA into the diet in the form of fish and seafood to maintain or improve metabolic health.

Conclusions

Overnutrition in any form poses a risk for obesity and fatty liver disease. The specific consequences of overnutrition on adipose tissue and liver, however, depend not only on the amount of energy consumed but also on the type and distribution of macronutrients that make up the diet. Carefully controlled experiments dissecting the impact of individual macronutrients on adipose tissue and liver have enabled their placement into a general rank order on the spectrum of harmful-to-benign. For carbohydrates this is fructose $>$ glucose $>$ starch $>$ fiber, based primarily on their bioavailability to and metabolism within the liver, and for fats the rank is saturated $\geq$ monounsaturated $>$ polyunsaturated, based on their ability to induce cytotoxicity and their potential to regulate DNL and fatty acid oxidation. The challenge is how to translate the information gained from these experimental studies to real-world situations in which diets are complex and ever-changing. As nutritional research continues, these challenges can be addressed, culminating in the development of sound nutritional guidelines for metabolic health.

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